A Systematic Review of Sellar and Parasellar Brown Tumors: An Analysis of Clinical, Diagnostic, and Management Profiles

Short Title: Sellar and Parasellar Brown Tumors

Authors

Mohamedkazim M. Alwani, MD [1, 4]

Gina N. Monaco, MD PhD [2, 4]

Sydney M. Harmon, BSK [4]

Obi I. Nwosu, BS [4]

Alexander O. Vortmeyer, MD [3, 4]

Troy D. Payner, MD [2, 4]

Jonathan Ting, MD MS MBA [1, 2, 4]

Author Affiliations

[1]Department of Otolaryngology – Head and Neck Surgery

[2]Department of Neurological Surgery

[3]Department of Pathology and Laboratory Medicine

[4]Indiana University School of Medicine

Corresponding Author

Mohamedkazim M. Alwani, MD, Department of Otolaryngology – Head and Neck Surgery

Indiana University School of Medicine,

1120 W. Michigan Street, Suite 400, Indianapolis, IN 46202

Telephone: 317-529-4351 | Fax: 317-274-8285 | Email: malwani@iupui.edu

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INTRODUCTION

Brown tumors are fibrovascular, expansile, lytic lesions that represent a tertiary manifestation of hyperparathyroidism.[1] With primary hyperparathyroidism, the autonomous release of parathyroid hormone (PTH) from a neoplastic, hyperplastic, or ectopic parathyroid nodule stimulates pathologic resorption of bone by osteoclasts leading to elevated serum calcium. On the other hand, secondary hyperparathyroidism occurs when chronically low serum calcium levels, for instance with calcium wasting in the setting of end-stage renal disease (ESRD), triggers a physiologically analogous elevation in PTH release with subsequent bone resorption in the attempt to restore serum calcium levels. The result of both primary and secondary hyperparathyroidism can be excessive bone resorption[2,3] which may terminate with the formation of brown tumors.[4,5]

Though the incidence of brown tumors as a consequence of hyperparathyroidism is rare, ranging between 1.5% to 3%[3,6], most of the existing literature details the occurrence of these lesions in the facial, thoracic, pelvic, and spinal skeleton.[4,5] Reports regarding involvement of the skull base, specifically the sellar and parasellar region, have remained exceedingly rare.[3] The varied clinico-diagnostic profiles reported in the already scarce literature preclude a well-founded consensus on the proper description, diagnostic workup, and/or management of these lesions. In this study, we report a patient with a histologically confirmed brown tumor in the clival region and provide a systematic review of past literature to evaluate clinical, diagnostic, and management trends.

METHODS

Case Report

A 51-year-old male presented to the Emergency Department (ED) complaining of a few weeks of neck pain. The patient's medical history was notable for ESRD for which he had been receiving dialysis for 4.5 years. Review of systems was remarkable for dysphagia and a sensation of fullness in the tongue. Physical exam revealed left tongue atrophy and mild diplopia. His visit to the ED was complicated by hyperkalemia due to a missed dialysis regimen, and he consequently suffered pulseless cardiac arrest from which he was successfully resuscitated. During his subsequent workup, laboratory testing revealed an elevated PTH of 1,385 pg/mL (normal range: 10 - 65) in the setting of normal serum calcium of 9.1 mg/dL (normal range: 8.4-10.2). At this juncture, a maxillofacial computed tomography (CT) scan without contrast was obtained and showed a lytic, expansile, and hyperdense mass involving the left clivus (**Figure 1a-b**). Magnetic resonance imaging (MRI) of the head with contrast showed a 4.2 cm by 1.5 cm enhancing mass of the left inferior clivus (**Figure 1c**).

A trans-nasal endoscopic approach was employed to resect the clival tumor. Histopathologic examination demonstrated multinucleated giant cells proliferating in a background of fibrovascular stroma with reactive bone formation (**Figure 2a-c**).

Following resection of the clival tumor, the patient was further evaluated for secondary hyperparathyroidism. Post-operative lab testing revealed normocalcemia in the setting of a persistently elevated PTH of 1,607pg/mL and a single-photon emission computed tomography (SPECT) scan revealed parathyroid hyperplasia. The patient received a total parathyroidectomy for definitive surgical management of his secondary hyperparathyroidism. Post-operative PTH testing confirmed reversal of hyperparathyroidism. The patient was discharged on post-operative day 1 on an appropriate calcium supplementation regimen. At his 1-month post-operative follow up, the patient reported complete resolution of his symptoms.

Systematic Review

We aimed to identify all full-text, peer-reviewed reports pertaining to brown tumors of the sellar/parasellar region. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting standard[7] served as a guideline for our review.

Eligibility criteria for inclusion and exclusion were determined prior to the literature search. Studies were included if they: (1) reported on sellar/parasellar brown tumors, (2) included key patient demographics and history findings, (3) provided key diagnostic findings including laboratory and imaging findings, (4) reported treatment modalities as well as follow-up data. Studies were excluded if they did not meet inclusion criteria and/or were: (1) a review of, or commentary on other pre-existing literature, (2) an editorial, (3) not written in English. Included articles were reviewed by two authors (M.A. and O.N.). On December 1, 2018, a thorough and comprehensive search of the PubMed, Ovid MEDLINE, Scopus, and Google Scholar databases was conducted to identify eligible studies. The search terms used included “brown tumors”, “sellar brown tumor”, “parasellar brown tumor”, and “clival brown tumor”.

The following information, when available, was extracted from the included reports: author, year of publication, patient demographics, character and duration of symptoms, abnormal lab values, imaging characteristics, histopathologic descriptions, management modalities, and follow-up data.

RESULTS

Study Selection

A summary of the PRISMA protocol is provided in **Figure 3**. A systematic search of PubMed, MEDLINE, Scopus, and Google Scholar databases yielded a total of 118 articles. Thirty-two (32) duplicate articles were removed leaving 86 articles eligible for preliminary title and abstract screening. After screening, 56 articles did not meet inclusion criteria and were thus excluded. The remaining 30 articles were subjected to a comprehensive full-text review. Subsequently, only 7 articles were eligible for final inclusion in the systematic review[3,6,8–12]. All frequency results are based on a total of 8 sellar/parasellar brown tumor cases (7 previously documented cases in addition to the current case report).

Demographics and Clinical Findings

The publication dates ranged from 1986 – 2014. A summary of the demographic and clinical profile of each reported case is provided in **Table 1**. All reported cases involved female patients, with the current reported case emerging as the only documented case of a sellar/parasellar brown tumor in a male patient. Patient age ranged from 18 to 59 years with a mean of 42.75 years. Five of eight cases provided a past medical history (62.5%), four of which were notable for ESRD (80%). Reported symptoms included visual disturbances such as decreased visual acuity or diplopia (n=6), headache (n=5), fatigue (n=3), nausea/vomiting (n=2), chest pain (n=1), neck pain (n=1), and dysphagia (n=1). Duration of symptoms ranged from 1 day to 24 months with a mean of 4.14 months. All reports provided a description of laboratory values. Laboratory findings included elevated alkaline phosphatase (ALP) (n=7), elevated PTH (n=6), hypercalcemia (n=5), azotemia (n=3), hypophosphatemia (n=2), hypocalcemia (n=2), anemia (n=2), hyperphosphatemia (n=1), and hyperchloremia (n=1). A summary of lab findings is also provided in **Table 1**.

Imaging and Histopathologic Findings

Reported preoperative imaging modalities included maxillofacial CT (n=6) and MRI head/neck (n=6), and skull radiographs (n=2). In all 6 cases where CT findings were provided, the sellar/parasellar lesions were noted to be expansile and lytic. Contrast enhancement was noted on 5 MRIs (83.3%) and hyperintensity was reported on T2-weighted (T2W) imaging in 4 MRIs (66.7%). Imaging modalities employed in concurrent workup of hyperparathyroidism included parathyroid ultrasound (n=2), parathyroid scintigraphy (n=2), MRI of the neck (n=2), bone scintigraphy (n=1), and SPECT scan (n=1). Histopathologic findings were reported in 7 of the reports (87.5%). Similar histology of multinucleated giant cells surrounded loose fibrovascular stroma was noted in all of these cases (as demonstrated in **Figure 2**). All imaging and histopathologic findings are detailed in **Table 2**.

Tumor Characteristics, Management, and Follow-Up Status

Tumor characteristics (location and size) are summarized in **Table 1**. All 8 reports documented the location of the brown tumor. Tumor locations reported included the sphenoid bone (n=7), occipital bone (n=2), parietal bone (n=1), and clivus (n=1). Two cases reported involvement of anatomic sites in addition to the skull base i.e. cervical spine and multiple lytic rib lesions, respectively. Tumor size was reported in 4 of the 8 case reports (50%) with a mean size of 3.1 x 3.0 x 2.5 cm.

Surgical management was reported in all 8 cases. Extirpation of the sellar/parasellar lesion was documented in 4 of the 8 cases (50%). A trans-nasal approach was employed in all 4 cases. The remainder received only endocrine surgery for management of hyperparathyroidism. Management information is summarized in **Table 1**.

Length of follow-up was documented in six of eight cases (75%) with a mean follow-up time of 1.3 years and a range of 0.5 to 3 years. All patients who received trans-nasal resection of their

sellar/parasellar lesions exhibited complete or significant symptom resolution. Symptom recurrence was noted in 1 case reported by Schweitzer et al.[9] Surgical complications related to endocrine surgery were noted in 2 cases[11,12], whereby patients experienced persistent hypocalcemia following parathyroidectomy. Both patients were successfully treated with calcium and vitamin D supplementation. No surgical complications from trans-nasal resections were reported.

DISCUSSION

Brown tumors are osteolytic, expansile lesions resulting from hyperparathyroidism that represent a tertiary fibro-osseous remodeling reaction rather than a true neoplasm.[6] Excess PTH in hyperparathyroidism drives osteoclastic and osteoblastic processes that subsequently cause bony resorption and fibro-osseous remodeling of the cortex and marrow.[8] Although these lesions were first described by Gerhard Engle in 1864[13], their association with hyperparathyroidism was reported later in 1905 by Askanazy.[3] However, this relation between brown tumors and hyperparathyroidism has been infrequently reported after the advent of biochemical testing for hypercalcemia and hyperparathyroidism. Since such testing has allowed for early detection and management of hyperparathyroidism, and given that brown tumors progress slowly and manifest late in the natural history of hyperparathyroidism, the overall incidence has decreased secondary to early intervention for hyperparathyroidism.[11]

Studies have found that the incidence of brown tumors is higher in primary hyperparathyroidism (usually caused by parathyroid adenomas or hyperplasia) at 3% to 5%, than in secondary hyperparathyroidism (usually caused by chronic renal failure or vitamin D deficiency) at 1.5% to 1.7%.[3,6] As was the case with the patient presented in our study, the authors agree with the hypothesis put forward by Kanaan et al suggesting that perhaps an increase in incidence of

brown tumors from secondary hyperparathyroidism may now be observed given the increased longevity of patients with ESRD due to improved dialysis technology and services.[3]

Brown tumors primarily occur in the mandible, clavicle, ribs, pelvis, and long bones such as the femur.[6,12] Although studies have reported involvement of the maxilla, palate, temporal bone, nasal cavity, and orbital bone in the craniofacial region, reports of sellar/parasellar brown tumors remain exceedingly rare.[6] Interestingly, and as demonstrated by our results, these limited reports of sellar/parasellar brown tumors show a tendency to occur in females (n=7, 87.5%), perhaps due to the higher incidence of hyperparathyroidism in females as compared to males.[14,15]

The clinical presentation of brown tumors varies depending on the anatomical site of the lesion. Sellar/parasellar brown tumors most commonly present with headaches and/or visual changes, but other symptoms including nausea, vomiting, and focal neurological deficits have been reported.[3,6,8–12] Histologically, brown tumors consist of multinucleated osteoclast-like giant cells in a spindle cell connective tissue stromal background. Large areas of bone resorption, hemorrhagic foci, and multifocal hemosiderin deposits represent degenerative changes that commonly occur in brown tumors.[6,8,12] Accumulation of hemosiderin imparts a reddish-brown tint to the lesions, giving the lesions their name (i.e. brown tumors).[3]

Key differential diagnoses for sellar/parasellar lesions often include invasive pituitary tumors, fibrous dysplasia, carcinomas, chordomas, chondrosarcomas, and neuroendocrine tumors.[3,16] The rarity of sellar/parasellar brown tumors generates a significant potential for misdiagnosis. Even at a histological level, the presence of giant cells necessitates a great deal of diagnostic astuteness to differentiate brown tumors of hyperparathyroidism from giant-cell reparative granulomas and true giant-cell tumors.[6]

Although the appearance of sellar/parasellar brown tumors on radiographs has not been classified, brown tumors in other anatomic areas classically exhibit widespread subperiosteal bone resorption.[10] This is consistent with the case reported by Erem et al that documented diffuse osteopenia with salt-and-pepper stippling seen on skull x-ray.[8] Radiographic findings were also reported by Takeshita et al where opacification of the sphenoid sinus was noted.[6] On CT imaging, sellar/parasellar brown tumors appear as lytic, expansile, and enhancing lesions, similar to brown tumors occurring in other regions of the body. The lytic and expansile nature of these lesions suggests a slow-growing process.[6] Although varying MR imaging characteristics have been reported for sellar/parasellar brown tumors, our review revealed a trend where by these tumors were often hyperintense on T2W and enhanced with contrast.[6,8,10,12] Heterogeneity was often reported on T2W images given the heterogenous pathological background these lesions consisting of hemorrhagic foci, hemosiderin deposits, and other cystic components.

The exceedingly rare nature of sellar/parasellar brown tumors has precluded the establishment of definitive therapeutic guidelines. Previous studies have advocated that the first step in management is to treat (either medically or surgically) the primary underlying endocrine etiology with the ultimate goal of achieving normalized lab values with ensuing spontaneous regression of brown tumors. However, the regression response with this strategy in sellar/parasellar lesion remains unclear, with reports showing minimal response[12] or even progression.[9] Therefore, in cases of larger brown tumors that are persistent and unresponsive to endocrine therapy, or in cases where acute deficits are present and lasting complications are possible, acute surgical decompression is indicated and favored. Our review of literature demonstrates that surgical extirpation yields favorable outcomes with complete symptom resolution noted in all patients who received surgical excision.

CONCLUSION

Sellar/parasellar brown tumors are a rare, tertiary manifestation of a common disease entity (i.e. hyperparathyroidism), and therefore can be elusive to diagnose. Appropriate, timely diagnosis (and consequent management) often requires a high index of clinical suspicion augmented by a complete workup including biochemical testing, imaging, and histopathologic analysis. Surgical removal of the skull base lesion is favored in the event that the lesion is causing compressive symptoms, or if it is unresponsive to management of hyperparathyroidism.

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FIGURE LEGENDS

Figure 1A: Axial maxillofacial CT without contrast demonstrating left clival brown tumor (arrow)

Figure 1B: Sagittal maxillofacial CT without contrast demonstrating clival brown tumor (arrow)

Figure 1C: Axial, T1-weighted, post-contrast MRI showing an enhancing left clival mass (arrow)

Figure 2. H&E-stained sections reveal focally preserved osteoid and large areas of bone resorption (**A**, 100x, measuring bar = 100 μm) characterized by multinucleated osteoclast-like giant cells and fibroblasts (**B**, 400x, measuring bar = 50 μm). Multifocal hemosiderin depositions (**C**, 400x, measuring bar = 50 μm) represent degenerative changes that commonly occur in brown tumors.

Figure 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of article identification and selection.

Table 1. Summary of patient information, medical and surgical management, and follow-up status.

Study	Age/Sex	Symptoms (Duration)	Abnormal lab values	Primary disturbance	Tumor location	Tumor size (cm)	Medical management	Surgical Management	Follow-up (Duration)
Schweitzer et al. 1986	46/F	Left frontal & retro-orbital headaches (6mo); Left diplopia and vision loss (1mo)	Hypercalcemia, elevated ALP	1º HPT due to parathyroid adenoma	Sphenoid sinus	NA	None	Resection of parathyroid adenoma following endoscopic and open biopsies of sellar lesion.	Despite normocalcemia, patient reported new-onset disequilibrium, tinnitus, and hearing loss in left ear. CT and histopathology revealed progression of BT (16mo)
Kanaan et al. 1998	21/F	Headache, nausea, vision impairment (4mo)	Hypocalcemia, hypochloremia, hyperphosphatemia, elevated ALP	2º HPT due to ESRD	Sphenoid sinus	NA	None	TNR of sellar lesion (1 month after decompression of lesion through a right lateral rhinotomy and external ethmoidectomy)	Minor post-op changes seen on MRI with dramatically improved vision (36mo)
Erem et al. 2004	47/F	Headache, dizziness, diffuse arthralgia & fatigue (24mo); Nausea & vomiting (6mo)	Anemia, elevated BUN & Cr, hypercalcemia, elevated ALP, elevated iPTH	1º HPT due to parathyroid adenoma	Sphenoid sinus and occipital bone	Sphenoid: 5 x 3.5 x 3.5cm Occipital: 3 x 2 x 2cm	None	Resection of right-inferior parathyroid adenoma	Complete symptom resolution with normalized labs except an elevated ALP (12mo)
Takeshita et al. 2004	47/F	Headache, left ptosis, and worsening right diplopia (3 days)	Elevated BUN and Cr, hypocalcemia, elevated ALP, elevated iPTH	2º HPT due to ESRD	Sphenoid sinus	NA	None	TNR of sellar lesion	Dramatic symptom relief (NA)
Yilmazlar et al. 2004	59/F	Headache, impaired vision in the right eye, and diplopia (5mo); Reduced vision and ptosis in left eye (1mo)	Hypercalcemia, hypophosphatemia, elevated ALP, elevated PTH	1º HPT due to parathyroid adenoma	Sphenoid sinus and parietal bone	Parietal: 1 x 2cm Sphenoid: NA	None	TNR of sellar lesion	Improved vision with normalized labs (8mo)
Lando HM 2012	18/F	Chest pain (NA)	Hypercalcemia, elevated ALP, elevated PTH	1º HPT due to parathyroid adenoma	Sphenoid sinus	3.4 x 4.7cm	None	Resection of parathyroid adenoma	Marginal regression of sphenoidal lesion to 3 x 4cm (18mo)
Loya-Solis et al. 2014	53/F	Bitemporal hemianopsia and diplopia, fatigue, generalized weakness, and somnolence (2mo)	Anemia, hypercalcemia, hypophosphatemia, hypomagnesemia, elevated ALP, elevated PTH	1º HPT due to parathyroid carcinoma	Sphenoid sinus	3 x 3 x 2cm	Hydration, furosemide, zoledronate	Left hemithyroidectomy & ipsilateral parathyroidectomy	Improved visual fields with normalized labs(6mo)
Present case, 2018	51/M	Neck pain, dysphagia, and sensation of fullness of tongue, 1 month	Elevated PTH	2º HPT due to ESRD	Left clivus & occipital condyle	2.9 x 1.6cm	None	TNR of clival lesion followed by total parathyroidectomy with auto-transplantation	Complete symptom resolution, with normalized labs (6mo)

ALP, alkaline phosphatase; BT, brown tumor; BUN, blood urea nitrogen; Cr, creatinine; ESRD, end-stage renal disease; F, female; HPT, hyperparathyroidism; iPTH, intact parathyroid hormone; NA, not available; PTH, parathyroid hormone; TNR, trans-nasal resection

Table 2. Summary of imaging, gross, and histopathologic findings.

Study	XR	CT	MRI	Histopathology	Parathyroid imaging
Schweitzer et al. 1986	NA	Expansile, lytic heterogenous sellar mass with remodeling of surrounding bone and involvement of cavernous sinus	NA	Diffuse fibrosis with mixed chronic inflammatory infiltrate	NA
Kanaan et al. 1998	NA	Expansile, lytic sellar mass with remodeling of surrounding bone and involvement of right orbit and posterior ethmoid sinus	Lesion morphology same as CT T1: Heterogenous hyperintense foci T2: Heterogenous hyperintense foci	Regenerative bone surrounded by fibrovascular stroma and multinucleated giant cells	NA
Erem et al. 2004	Diffuse osteopenia and subperiosteal resorption, salt-and-pepper stippling in the skull	NA	Expansile, lytic sellar mass eroding into medial wall of right orbit and posterior ethmoid sinus T1: Contrast enhancing T2: Hyperintense	Multinucleated giant cells surrounded by fibrovascular stroma with focal hemorrhages and hemosiderin-laden macrophages as well as focal sites of reactive woven bone formation	Parathyroid U/S revealed a 26 x 18mm heterogenous mass at posterior-inferior right thyroid lobe MRI of neck showed hyperintensity in the same area Histopathologic examination of resected mass revealed parathyroid adenoma
Takeshita et al. 2004	Opacification of the sphenoid sinus	Expansile, lytic heterogenous sellar mass with remodeling of surrounding bone	Lesion morphology same as CT T1: Isointense, contrast enhancing T2: Heterogeneously hyperintense	Multinucleated giant cells, loose fibrous stroma with spindle-shaped mononucleated cells, focal hemorrhage and hemosiderin deposition	NA
Yilmazlar et al. 2004	NA	Expansile, lytic sellar mass with remodeling of surrounding bone and involvement of posterior ethmoid sinus; Distinct lytic lesion in noted in right parietal bone	Lesion morphology same as CT T1: Isointense, contrast enhancing T2: Hyperintense, contrast enhancing	Central osteoclasts with focal areas of fibroblasts and hemorrhage	MRI of neck revealed a T1 hypointense, T2 hyperintense left inferior parathyroid lesion; Parathyroid scintigraphy revealed an adenoma in the same area; Bone scintigraphy displayed increased activity in proximal right radius, parietooccipital area, and left tibia
Lando HM 2012	NA	NA	Sellar mass with involvement of optic chiasm and cavernous sinus T1: NA T2: “Markedly dark”, contrast enhancing	NA	Parathyroid U/S revealed a heterogenous parathyroid mass; Histopathologic examination revealed parathyroid adenoma
Loya-Solis et al. 2014	NA	Expansile, lytic heterogenous sellar mass with remodeling of surrounding bone and erosion the sphenoid corpus	NA	Multinucleated giant cells in fibrous stroma with hemosiderin deposition	Parathyroid U/S and scintigraphy revealed enlarged right inferior parathyroid gland and hyperfunction; Histopathologic examination of resected parathyroid gland was diagnostic of parathyroid carcinoma
Present case, 2018	None	Expansile, lytic heterogenous sellar mass with remodeling of surrounding bone with involvement occipital condyle	T1: hypointense, contrast enhancing T2: hyperintense	Giant cell proliferation and hemosiderin deposits in a spindle stromal connective tissue background	SPECT scanning revealed parathyroid hyperplasia

CT, computed tomography; MRI, magnetic resonance imaging; NA, not available; SPECT, single-photon emission computed tomography; U/S, ultra-sound

Figure 1A: Axial maxillofacial CT without contrast demonstrating left clival brown tumor (arrow)

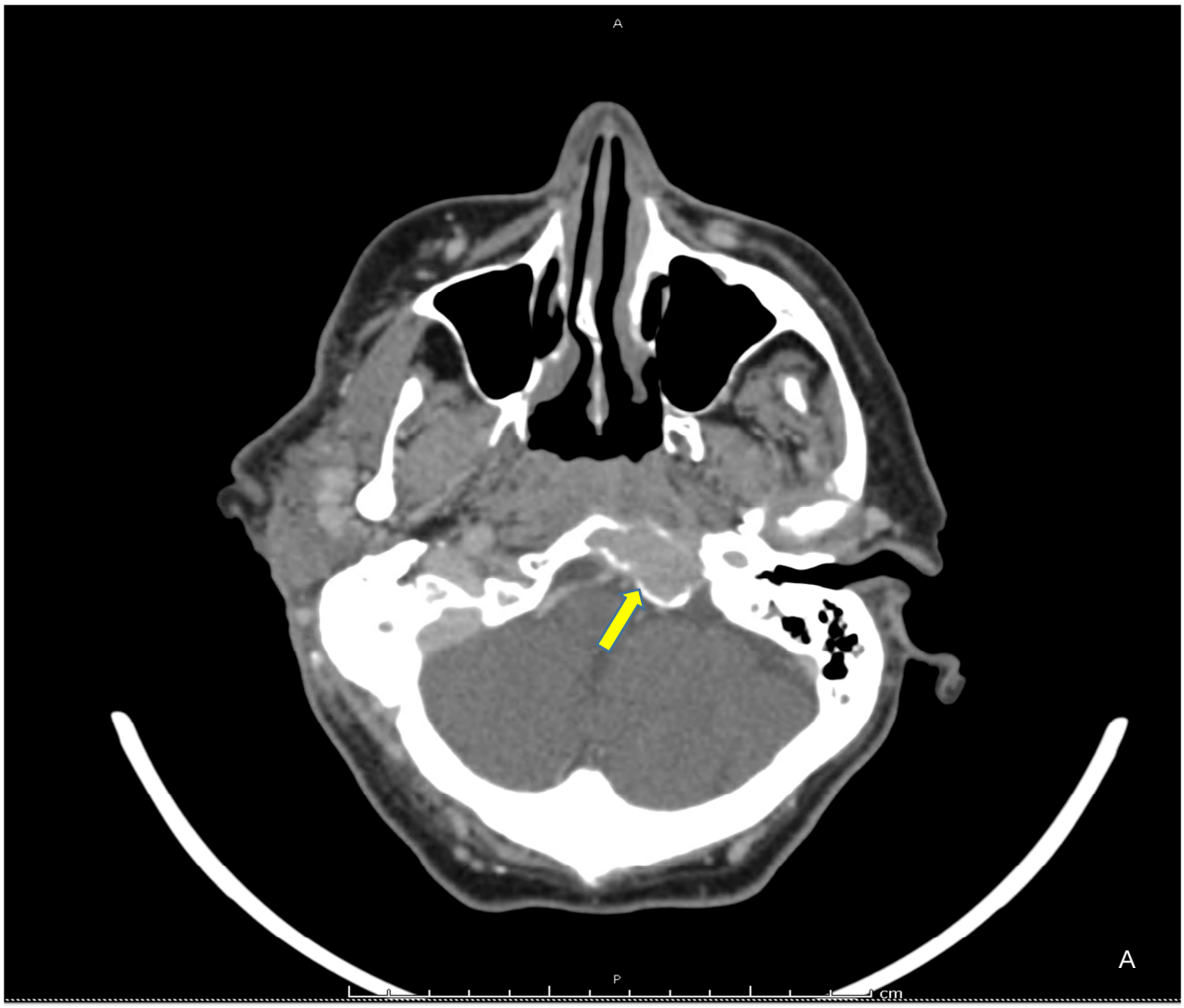


Figure 1B: Sagittal maxillofacial CT without contrast demonstrating clival brown tumor (arrow)

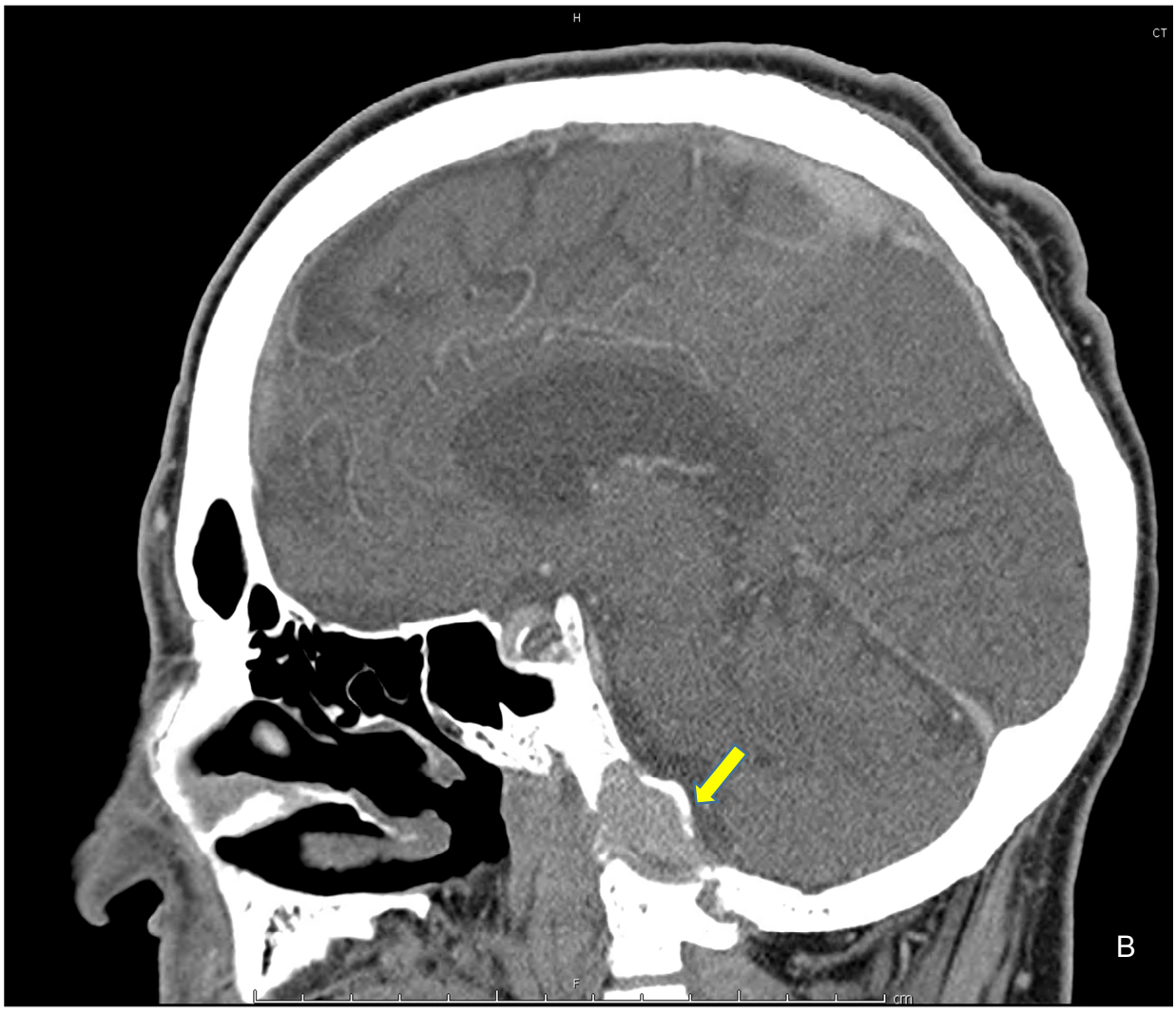


Figure 1C: Axial, T1-weighted, post-contrast MRI showing an enhancing left clival mass (arrow)

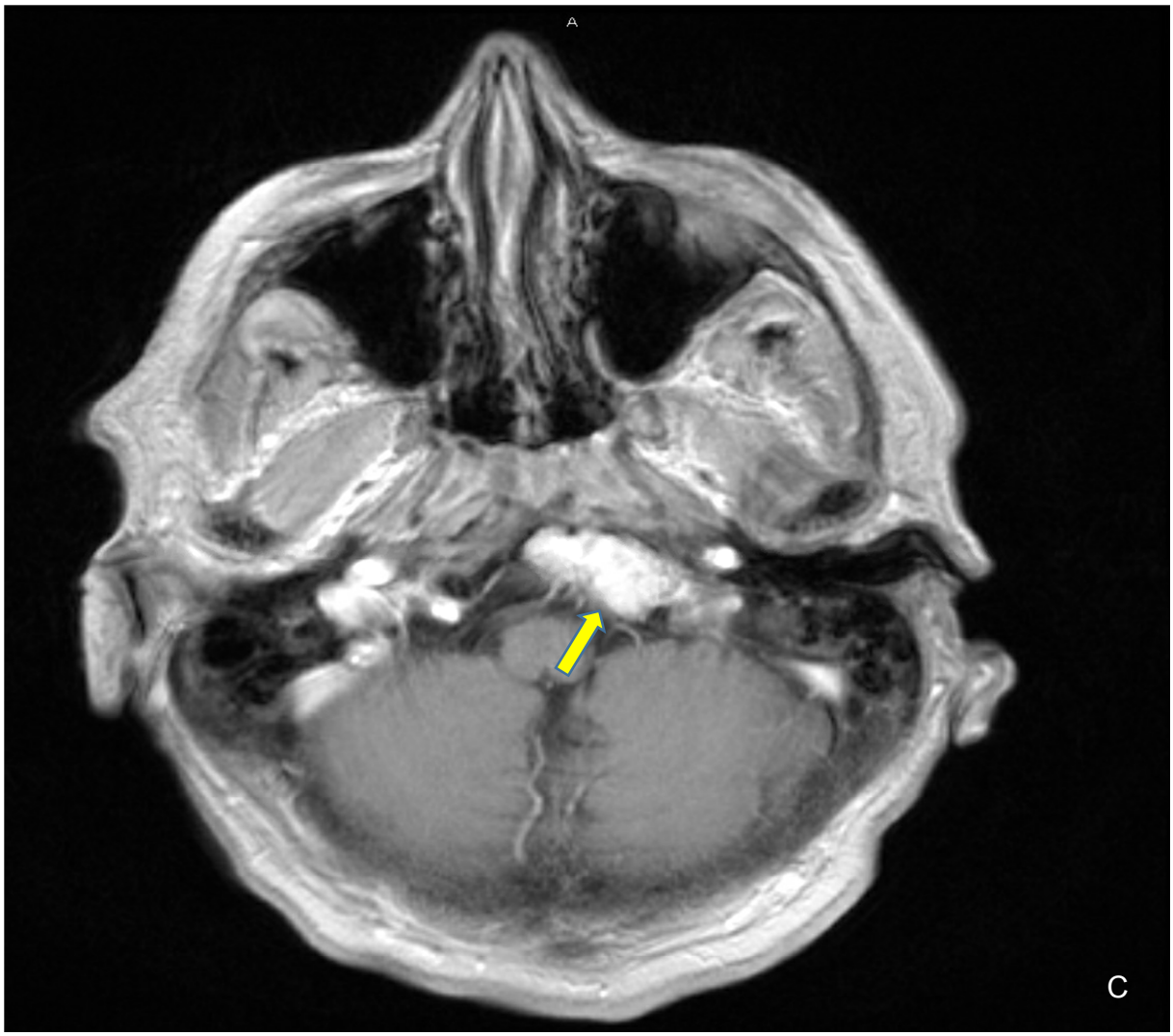


Figure 2. H&E-stained sections reveal focally preserved osteoid and large areas of bone resorption (**A**, 100x, measuring bar = 100 μm) characterized by multinucleated osteoclast-like giant cells and fibroblasts (**B**, 400x, measuring bar = 50 μm). Multifocal hemosiderin depositions (**C**, 400x, measuring bar = 50 μm) represent degenerative changes that commonly occur in brown tumors.

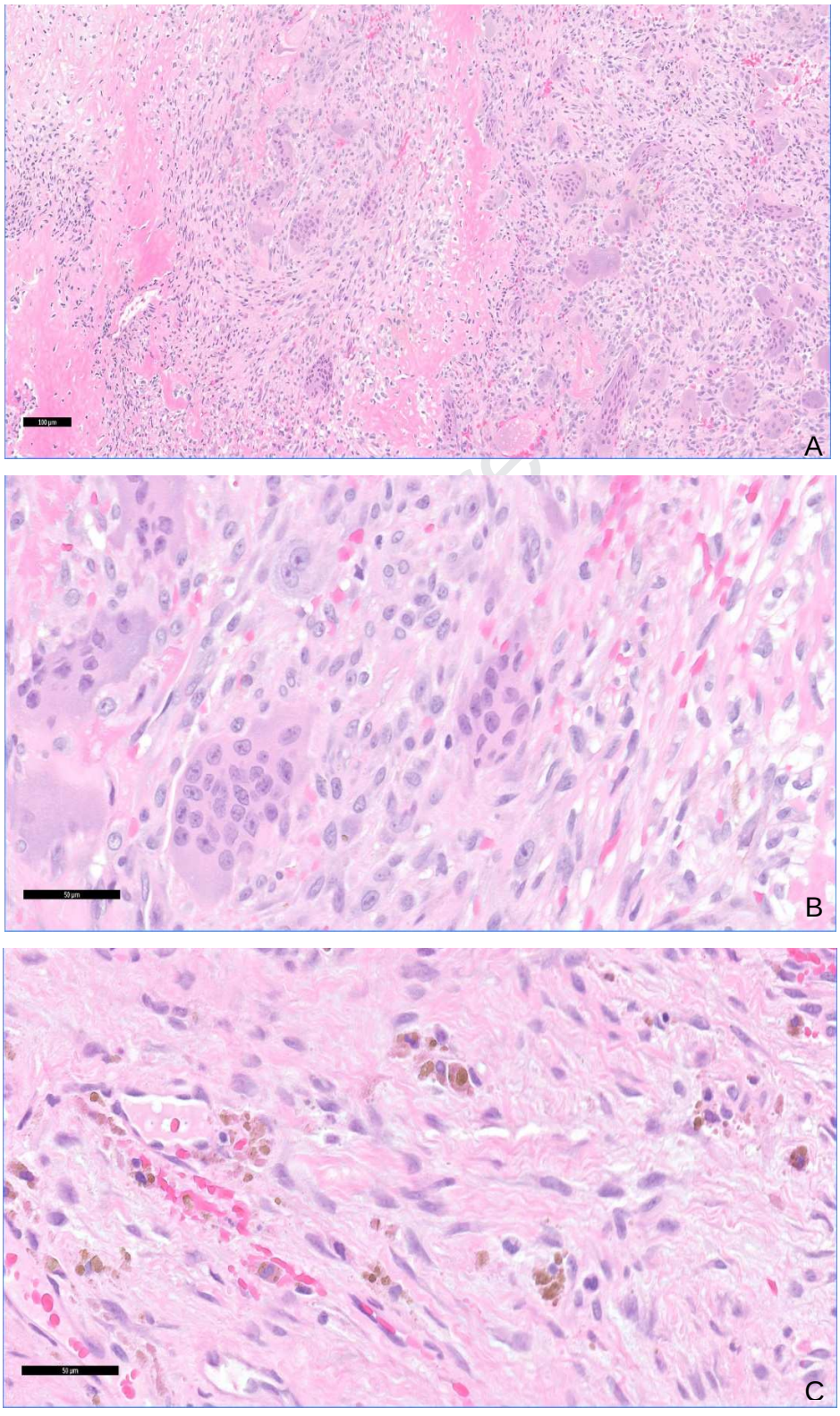
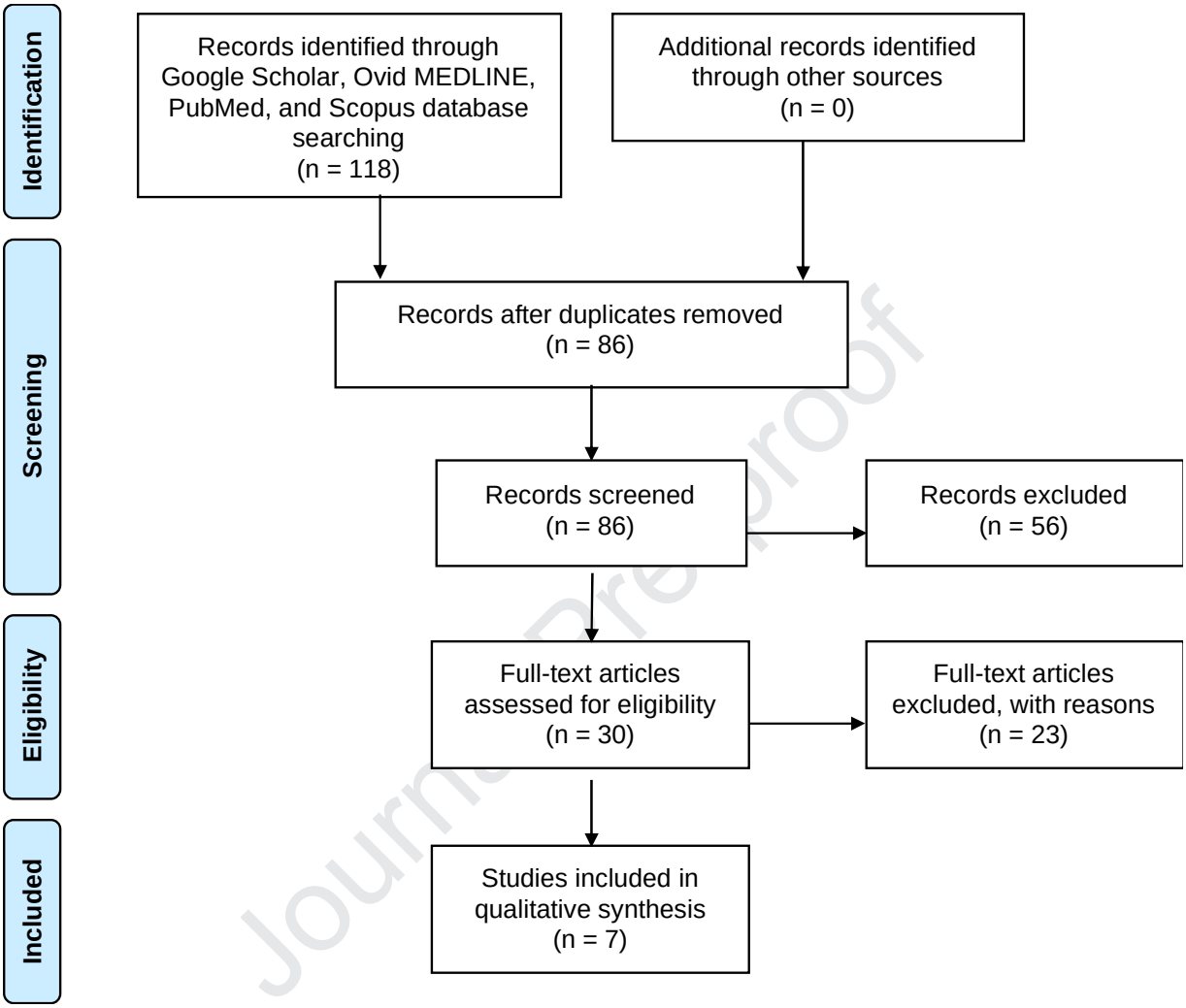


Figure 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of article identification and selection.



ABBREVIATIONS

ALP	-	Alkaline Phosphatase
CT	-	Computed Tomography
ED	-	Emergency Department
ESRD	-	End Stage Renal Disease
MRI	-	Magnetic Resonance Imaging
PRISMA	-	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH	-	Parathyroid Hormone
SPECT	-	Single Photon Emission Computed Tomography